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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,993	CHANG ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/13/06 and 28 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-66* is/are pending in the application.

4a) Of the above claim(s) *16,17,22-24 and 27-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-15,18-21,25 and 26* is/are rejected.

7)☒ Claim(s) *7-10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/18/06; 10/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Applicant's amendment filed on September 18, 2006, has been received and entered. Claims 1-26 have been amended, while applicants have also added claim 66.

Election/Restrictions

Applicant's election with traverse of the invention of claims 1-26 (group I) filed September 18, 2006 is acknowledged. The traversal is on the grounds(s) that Examiner has not set forth convincing argument that the search and examination of group I and other groups such as II and III necessarily represents an undue burden for the examiner and that examination of all the groups would not require separate searches for prior art. Applicant argument for examining other groups (II, III) is not persuasive because the inventions are distinct, each from the other because inventions of group I and II are related as product and process of use. In the instant case, the product can be used in methods of delivery, and the process of making a protein can be practiced with other bacterium or Lactobacillus. In addition, Lactobacillus of group I contains a materially different expression cassette. Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art in view of their different classification, and the inventions require a different field of search (see MPEP

§ 808.02), restriction for examination purposes as indicated is proper. Additionally, the different inventions have different status in the art because they are drawn to different structure and functions. It is noted that newly added claim broadly reads on a method as recited in invention of group II. Thus, claim 66 is also included in invention of group II. It is noted that applicants have indicated election of 2D-CD4 as species for examination in a supplementary response filed on 12/ 28/2006.

The requirement is still deemed proper and is therefore made FINAL.

Claims 27-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. It is noted that claims 16-17, 22-24 do not read on elected species and therefore claims 16-17, 22-24 are also withdrawn. Applicant timely traversed the restriction (election) requirement in the reply filed on September 18, 2006.

Claims 1-5, 7-15, 18-21 and 25-26 are under examination.

Claim Objections

The claims 7-10 are objected to because they do not comply with the sequence rules. Appropriate correction is required. Failure to comply with the sequence rules will be considered non-responsive.

It is noted that claims 7-10 contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) as follows: The claims recites plurality of

amino acid sequence that is not identified by any Sequence identification number (see claims 7-10).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-15, 18-21 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Lactobacillus jensenii* bacterium comprising an expression cassette; wherein said expression cassette comprising a promoter operably linked to polynucleotide encoding a signal sequence and a biologically-active polypeptide, wherein the biologically active polypeptide is 2D-CD4 that is linked to a heterologous carboxyl terminal cell wall targeting region comprising cell wall anchor sequence selected from the list consisting of C14 and C370 and more specifically set forth in the examples, does not reasonably provide enablement for any other microorganism comprising any other biologically active polypeptide or cell wall associated sequences . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by

weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

The claimed invention is directed to a genetically modified *Lactobacillus jensenii* that is vagina-colonizing strain comprising an exogenous gene encoding the biologically active protein. It is noted that dependent claims limit the cell wall targeting region comprising plurality of anchoring sequences. Claims 15, 18-21 limit the biologically active protein that binds to pathogen when contacted with the pathogen subsequently limiting to HIV pathogen. Claims 20 and 21 limit the biologically active protein to include CD4 subsequently limiting to include 2D-CD4.

The aspects considered broad are: the breadth of biologically active polypeptide simply being expressed on the surface of bacterium, inserting any biologically active protein into the cell wall, and any combination of anchor motif of any length in claims.

The instant specification and the prior art provide sufficient guidance to indicate that surface expression of proteins via covalent linkage with peptidoglycans in Gram-positive bacteria involves unique sorting signals and sortase-dependent machinery. The prior art also teaches plurality of genetically modified bacterium for the expression of biologically active protein (see US patent 6,190,662, dated 2/20/2001 and WO 96/11277). The specification teaches that the all the three cell wall anchored proteins identified after genomic sequencing of *L. jensenii* 1153 have LPQTG sorting signal preceding a hydrophobic region and a charged C-terminal tail and possess unique long repetitive sequences (see figure 1 of the specification). In addition, instant specification has exemplified a stretch of 95 amino acids containing one tandem repeat in fusion with the C-terminal cell wall sorting signal in pOSEL268 (Examples and see Figure 7) enables surface display of CD4 in *Lactobacillus jensenii.*

The specification provides guidance with respect to a genetically modified *Lactobacillus jensenii* comprising an expression cassette comprising a promoter operably linked to polynucleotide encoding a signal sequence and a biologically active polypeptide, wherein the biologically active polypeptide is 2CD4 linked to a heterologous carboxyl terminal cell wall targeting region. However, it does not provide specific information required by the Artisan to reasonably predict a *Lactobacillus jensenii* comprising any biologically active protein inserted into the cell wall will express

the protein at the surface and not adversely affect the assembly of the cell wall. In addition, breadth of instant claims embrace cell wall targeting region comprising cell wall associated sequence of any length. Applicants do not enable a *L. jensenii* expressing plurality of biologically active polypeptide on the surface as broadly claimed.

Claims 1-28 embrace a genetically modified *Lactobacillus jensenii* expressing biologically active protein. The specification contemplates biologically active protein refers to any amino acid sequence that has the biological activity of the amino acid sequence within, or outside of, a native cell (see para 35 of the published application). In addition, specification contemplates polypeptides of the invention can be of any size and molecular weight (See para. 112). The specification has exemplified *Lactobacillus jensenii* expressing 2-CD4 on the surface (see example and para 115 of the published application). Prior to instant invention, it is art recognized that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The claims embrace any biologically active polypeptide or fragment of CD4. It is noted that mere identification of critical regions such as one for the fragment of CD4 would not be sufficient, as the ordinary artisan would immediately recognize that the polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. (see Rudinger in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976, Guo et al, PNAS 101425): 9205-9210, 2004). This is also evidenced by studies of Ngo et al that disclose

addition of polypeptides, which are critical to maintain the protein structure/function, will require guidance (Ngo et al., 1994, The protein Folding Problem and Tertiary Structure Prediction, pp492-495). Prior to instant invention, Davis, (New Biologist, 1990, 2(5), 410-419) teaches that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid. These observations are further supported by the studies of Skolnick et al (Trends in Biotech, 2000,18, 34-39) describing, "..sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (abstract). Skolnick further states that "knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (page 36, column 1, box 2). Therefore, It is apparent from the cited arts that biological function of a protein, peptide or its fragments were unpredictable at the time of the invention and even same short stretch of amino acid sequence could show diverse biological functions while surrounded by different background amino acid sequences. In the instant case, claims are directed to a

genetically modified bacterium that expresses any biologically active protein of any size. The specification does not adequately provide structure function relationship of adequate number of molecule that would be capable of performing the function embraced by the claims. The breadth of these claims embraces numerous different unidentified peptides, proteins that are biologically active. Absent of evidence to the contrary, it is not clear that whether any biologically active protein of any size would be functional in same manner as they have been demonstrated for 2D-CD4. Thus, the art of record at the time of the invention does not provide enabling support commensurate with full scope for the claimed invention other then a *L. jensenii* expressing 2CD4. An artisan would have to perform undue experimentation to empirically test by trial and error different nucleic acid encoding protein to practice the *L. jensenii* comprising diverse group of biologically active protein as broadly recited in the instant claims

Claims are also directed to a genetically modified *L. jensenii* comprising a cell wall targeting region. The specification teaches that the cell wall associated sequence comprises at least 50 amino acids or comprises at least 200 amino acids (see paragraph 17). It is noted that specification describe the length of the cell wall associated region may vary. The cell wall associated region is typically between 40 and 1,000 amino acids. It is noted that specification describe presence of a stretch of 95 amino acids containing one tandem repeat in fusion with the C-terminal cell wall sorting signal in *Lactobacillus jensenii* (see paragraph 72 of the specification). It is also noted that specification illustrates that the C-terminal anchor motif of 36-amino acid in length is insufficient to drive surface expression of 2D CD4 (see Figure 6). Prior to instant

invention, Pancholi et al (J. Bacteriol. 1988, 170:2618-2624) teach presence of around 50 amino acids long cell wall associated sequence in M6 protein of *S. pyogenes,* while Strauss et al (Mol. Microbiol. 1996, 21:491-500) describe presence of about 90 amino acids in *S. carnosus*. Thus, it is not apparent how cell wall targeting region of any size and specifically less than 50 amino acid sequence would be functional in expressing any biological active protein as broadly embraced by instant claims. It is noted that prior art as well as instant specification provide any specific guidance in this regard. The skilled artisan would have to empirically test different carboxy -terminal cell wall targeting region and successful binding of the plurality of biologically active protein or fragment, and the stability of the protein produced, and extent of protein production at the surface. It is noted that there is no evidence that *L. jensenii* comprising a cell wall targeting region of any length would be functional to express any protein. The applicant's disclosure does not enable one skilled in the art to practice the invention commensurate with full scope without further undue amount of experimentation, which requires the identification and characterization to empirically test different cell wall targeting region for contemplated biological activity.

In conclusion, in view of breadth of the claims and absence of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions commensurate with full scope of the claim. The specification and prior art do not teach a genetically modified *L. jensenii* comprising any biologically active polypeptide linked to any heterologous carboxy terminal cell wall targeting region commensurate with full scope of the claims.

An artisan of skill would have to perform undue experimentation to practice the composition as claimed because the art of expressing any protein from genetically modified bacterium using any heterologous carboxy terminal cell wall targeting region was unpredictable at the time of filing of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 112-Written Description

Claims 1-5, 7-10, 13-15, 18-21 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim embraces a heterologous carboxy terminal cell wall targeting region comprising a cell wall associate sequence.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1 117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The cell wall targeting sequence and cell wall associated sequence, encompassed within the genus of polypeptide and cell wall associated sequence. Based upon the prior art there is expected to be sequence variation of signal sequence or cell wall associated sequence. The specification teaches that the cell wall associated sequence comprises at least 50 amino acids or comprises at least 200 amino acids (see paragraph 17). It is noted that specification describe the length of the cell wall associated region may vary. In addition, specification discloses in *Lactobacillus jensenii*, a stretch of 95 amino acids containing one tandem repeat in fusion with the C-terminal cell wall sorting signal in pOSEL268 (see paragraph 72 of the specification). The specification teaches that LPQTG motif are critical sorting signal within the cell wall anchor sequences C14 and C370. The specification also teaches the importance of P and T within the LPQTG sequence and other point mutations within the LPQTG motif on both C14 and C370 sequences to determine the effect of mutagenesis of LPXTG (see para 156 and 157 of the specification). The specification has provided the description of SEQ ID NO: 5- 8. However, specification fails to provide any specific guidance the size of cell wall targeting region or cell wall associated sequence. It is emphasized that an addition or deletion of amino acid from critical region in conjunction with any biologically active polypeptide that is linked to the cell wall targeting region may not show contemplated biological activity. This is particularly critical as protein is highly dependent on the overall structure of the protein itself and the primary amino acid sequence determines the conformation of the protein. This is also evidenced by studies of Ngo et al that disclose addition or deletions, which are critical to maintain the protein

structure/function, will require guidance. The mere identification of critical regions would not be sufficient, as encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. (Ngo et al., 1994, The protein Folding Problem and Tertiary Structure Prediction, pp492-495). Thus, it is apparent that a minor structural difference in compositions could result in substantially different activities. The specification however has not disclosed the addition or other region of any length of cell wall targeting region that would be functional to express any protein at the surface of the bacterium. The specification does not teach any cell wall targeting region or cell wall associated sequence that is 50 or less amino acid as required by independent claims that would show contemplated biological activity. The claimed invention as a whole is not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics. Inc.*, 48 USPQ2d 1641, 1646 (1998). The specification fails to describe what sequence of cell wall targeting regions other than exemplified in the specification fall into the genus that has contemplated biological activity. The skilled artisan cannot envision the detailed chemical structure of the all the sequences showing contemplated biological activity, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the composition.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 UsPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In view of the above considerations, one of skill in the art would not recognize that applicant was not in possession of the necessary common features or attributes possessed by member of the genus of cell wall targeting regions or cell wall associated sequence, other than the ones exemplified in the specification. Therefore, Applicant was not in possession of the genus of cell wall targeting regions or cell wall associated sequence as encompassed by the claims. *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-15, 18-21 and 25-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 is vague and indefinite because it is not clear how the sequence is associated with cell in the cell wall targeting region. It is unclear whether these sequences are associated with cell wall by another sequence or some other type of chemical bonding. Claims 2-5, 7-15, 18-21 and 25-26 directly or indirectly depend on claim 1. Appropriate correction is required.

Claim 4 is indefinite to the extent it recite a limitation to include "further comprises a charged sequence at the carboxy terminus of region". It is noted that carboxy terminal cell wall region of claim 1 comprises a hydrophobic sequence which is a charged sequence. Thus, claim 4 is not further limiting to claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5, 13-14 and 25-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Tagliabue et al (WO 96/11277, IDS) as evidenced by Steidler et al (US patent 6,190,662, dated 2/20/2001).

The claims embrace *Lactobacillus jensenii* comprising a sequence that encodes a heterologous protein comprising a promoter operably linked to a polynucleotide encoding a biologically active polypeptide linked to a cell wall targeting region comprising cell wall associated sequence, LPQ(S/A/T)(G/A) and hydrophobic sequence. Tagliabue et al that teach plurality of recombinant bacterium including *Lactobacillus* for producing biologically active polypeptide for delivering recombinant bacterium for expressing biologically active protein to a mucosal surface including vagina. It is noted that Tagliabue et al contemplated recombinant *Lactobacillus* including *Lactobacillus jensenii* and *L. Lactis* (see Tagliabue et al, pages 8-10, especially page 10, line 25). In addition, prior art as evidenced by Steidler et al teach a method to transform Gram-positive host organism with a recombinant vector. Steidler et al disclose a recombinant *Lactococcus lactis* comprising a chimeric gene containing nucleic acid encoding a secretion signal sequence, a desired protein or polypeptide and a cell wall attachment domain, such as that derived from *Staphylococcus aureus* protein A of the LPXTG motif. It is noted that Steidle contemplated cell wall anchoring domain comprises, at the C-terminal, anchoring domain derived from the *Staphylococcus aureus* protein A, however, other proteins could also be used as the cell wall anchoring domain. Thus, it is clear that Seidler contemplate any heterologous anchoring domain as long as they have properties of being stably bound to the surface of the cell and are capable of representing the desired protein on the cell surface. Thus, disclosure of Tagliabue et al directed to genetically modified *Lactobacillus jensenii* would embrace the entire necessary element known in the art to express protein and as evidenced from the

teaching of Seidler. It is emphasized that different anchor cell wall sorting signal sequences are inherently present in gram-positive bacterium including *Lactobacillus jensenii.* Thus, recombinant *Lactobacillus jensenii* disclosed by Tagliabue et al and those embraced by the instant claims appear to be structurally same. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Accordingly, claims 1, 4-5, 13-14 and 25-26 are anticipated by Tagliabue et al (WO 96/11277).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 13-14 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue et al (WO 96/11277, IDS), Steidler et al (US patent 6,190,662, dated 2/20/2001), Schneewind et al (US patent application, 20060073530, dated 4/6/2006, filing date 8/15/2002, effective filing date 8/15/2001).

Tagliabue et al that teaches plurality of recombinant bacterium including *Lactobacillus* for producing biologically active polypeptide for delivering recombinant bacterium for expressing biologically active protein to a mucosal surface including vagina. It is noted that Tagliabue et al contemplated recombinant *Lactobacillus* including *Lactobacillus jensenii* and *L. Lactis* (see Tagliabue et al, pages 8-10, especially page 10, line 25). Thus, it is clear that LPQTG anchor cell wall sorting signal sequences are inherently present in gram-positive bacterium including *Lactobacillus jensenii.* However, Tagliabue differed from claimed invention by not disclosing other signal sequence for expression of protein.

Steidler et al teach Gram-positive host organism transformed with a recombinant vector, such as *Lactococcus lactis* comprising a chimeric gene containing nucleic acid encoding a secretion signal sequence, a desired protein or polypeptide and a cell wall attachment domain, such as that derived from *Staphylococcus aureus* protein A of the LPXTG motif (see col. 2, lines 46-53). It is noted that Steidler contemplated cell wall anchoring domain comprises, at the C-terminal, anchoring domain derived from the *Staphylococcus aureus* protein A, however, other proteins could also be used as the cell wall anchoring domain. Thus, it is clear that Seidler contemplate any heterologous anchoring domain as long as they have properties of being stably bound to the surface

of the cell and are capable of representing the desired protein on the cell surface. Steidler also teach that the Gram-positive host organism of *Lactococcus* host would express desired protein and are covalently attached to the cell wall and is displayed on the outer face of the surface of the host organism (see entire col. 2). It is noted that Seidler et al also disclose that nucleic acid encoding the fusion protein is operably linked to control sequences to direct its expression (see col. 4, 22-32). Seidler taught a Gram-positive host more specifically *Lactococcus lactis* bacterium comprising the entire claimed element, but Seidler differed from claimed invention by not teaching *Lactobacillus jensenii*.

Schneewind teach different motifs that can be employed in expressing a polypeptide of interest on the surface of bacteria that are recognized by Srt A or Srt B (See para. 11 of the publication) including LPQTG EESNKDMTLPLMALLALSSIVAFVLP RKRKN SEQ ID NO. 25 (see table 1 and para 54). Schneewind contemplated that the sorting signal may include all or part of the sequences NPQ/KTN/G or LPX3X4G, where X3 is any of the 20 naturally occurring amino acid and X is an alanine, serine, or threonine (see para. 166 of the published application). It is noted that Schneewind generally embraced the idea of a polypeptide with a sorting signal with a LPX3X4G motif that may further include hydrophobic domain of at least 31 amino acids carboxyl to the motif and a charged tail region (see para. 20), he did not teach a genetically modified *Lactobacillus jensenii* expressing any polypeptide.

Accordingly, in view of the teachings of Tagliabue et al, Schneewind and Steidler, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the recombinant *Lactobacillus jensenii* disclosed by Tagliabue to include expression cassette comprising a promoter operably linked to polynucleotide encoding a signal sequence and biologically active polypeptide that is anchored to a cell wall targeting region as disclosed by Steidler and Schneewind with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Steidler had generally embraced the idea of expressing polypeptide on the surface of gram-positive bacterium (supra) and particularly since Tagliabue et al sought to create recombinant *Lactobacillus jensenii* for expressing biologically active protein to a mucosal surface. Schneewind provided motivation to determine different motifs that can be employed in expressing a polypeptide of interest on the surface of bacteria that are recognized by Srt A or Srt B (See para. 11 of the publication) including LPQTG Therefore, given that different genome sequencing and homology searches of different strains of gram positive bacteria were available to one of ordinary skill in the art and other motifs such as LPQTG were employed in expressing a polypeptide of interest on the surface of bacteria as per the teachings of Schneewind. It would have obvious for an artisan of ordinary skill in the art to use LPQTG as cell wall anchor sequence as disclosed by Schneewind with other elements disclosed by Steidler to create genetically modified *Lactobacillus jensenii* as disclosed in the instant application.

One who would practiced the invention would have had reasonable expectation of success because Tagliabue et al had already described *Lactobacillus* for producing biologically active polypeptide for delivering recombinant bacterium for expressing biologically active protein to a mucosal surface including vagina. Schneewind and Steidler provide necessary elements and motivation to express protein on other Gram-positive bacterium. Thus, it would have only required routine experimentation to modify the composition disclosed by Tagliabue to include other sorting signal and elements as disclosed Schneewind and Steidler and as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-5, 7-10, 13-14 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue et al (WO 96/11277), Steidler et al (US patent 6,190,662, dated 2/20/2001), Schneewind et al (US patent application, 20060073530, dated 4/6/2006, filing date 8/15/2002, effective filing date 8/15/2001) and Navarre et al (Microbiol Mol Biol Rev. 1999; 63(1): 174-229, IDS).

The combined teaching Tagliabue et al, Schneewind and Steidler have been discussed above and relied in same manner here. However, none of the references teaches other cell wall targeting regions.

Prior to instant invention, art teaches that most cell wall anchored proteins from Gram-positive bacteria share the same sorting signal LPXTG, some of the proteins, however, have different motifs. Navarre et al disclose that the LPXTG motif is

conserved within the sorting signals of all known wall-anchored surface proteins of gram-positive bacteria (see Table 1). It is noted that Navarre teach that threonine (T) displays some variation in that either alanine or serine can be found at this position. In addition, Navarre discloses a threonine-to-alanine substitution in the sorting signal of staphylococcal protein A and resulting mutation showing no affect in anchoring suggesting that these sequences could be functional sorting signals. In addition, Navarre also discloses other mutations such as a proline (P)-to-asparagine (N) mutation, resulting in abolishment of sorting signal. These suggest that proline being the critical element and cannot be substituted with any other amino acid residue (see page 184, col. 1, para. 2). However, Navarre et al differed from claimed invention by not disclosing genetically modified *Lactobacillus jensenii.*

Accordingly, in view of the teachings of Tagliabue et al, Schneewind, Steidler and Navarre, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the recombinant *Lactobacillus jensenii* disclosed by Tagliabue to include expression cassette comprising a promoter operably linked to polynucleotide encoding a signal sequence and biologically active polypeptide that is anchored to a cell wall targeting region comprising different signal sequence as disclose by Navarre and Schneewind with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Schneewind, and Navarre taught that Gram-positive bacteria sorting signal LPXTG is mostly conserved but some however, have different motifs. Given that different genome, sequencing and homology searches of different strains of gram

positive bacteria including *Lactobacillus jensenii* were available and routine to one of ordinary skill in the art. It would have been prima facie obvious to one of ordinary skill in the art to use other motifs such as LPQTG to express polypeptide of interest on the surface of bacteria as per the teachings of Schneewind. In addition, Navarre disclosed importance of other amino acid at different positions in optimizing protein expression and also indicated the necessity proline (P) (surap) which cannot be substituted with any other amino acid residue. It would have obvious for an artisan of ordinary skill in the art to use LPQTG as cell wall anchor sequence as disclosed by Schneewind on the basis with other elements disclosed by Steidler to create genetically modified *L. jensenii* as disclosed in the instant application. Tagliabue et al, Schneewind, Steidler and

One who would practiced the invention would have had reasonable expectation of success because Tagliabue et al had already described *Lactobacillus* for producing biologically active polypeptide for delivering recombinant bacterium for expressing biologically active protein to a mucosal surface including vagina. Schneewind and Steidler and Navarre provide necessary elements and motivation to express protein on other Gram-positive bacterium using different cell wall associated sequence to optimize the protein expression as per the teaching of Navarre.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-5, 7-10, 13-15, 18-21 and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue et al (WO 96/11277), Steidler et al (US patent

6,190,662, dated 2/20/2001); Schneewind et al (US patent application, 20060073530, dated 4/6/2006, filing date 8/15/2002, effective filing date 8/15/2001) Boyd (US 6,193,982, IDS) and Vallor et al. (The Journal of Infectious Diseases, 184:1431-6, 2001, IDS).

The combined teaching Tagliabue et al, Schneewind and Steidler have been discussed above and relied in same manner here. However, none of the references teach a genetically engineered *Lactobacillus jensenii* comprising a nucleotide sequence encoding CD4 or an HIV-binding fragment of CD4, wherein CD4 or an HIV-binding fragment of CD4 bind to HIV.

However, at the time the invention was made, Boyd teaches that cyanovirin-N, which binds to gp120 of immunodeficiency virus, can be used treat viral infections (columns 4, 6-7, and 15). Cyanovirin-N is an 11kDa protein. Boyd teaches that exploiting the HIV gp120-targeting properties of sCD4 (also known as two-domain soluble CD4 protein) was known to one of ordinary skill in the art (column 10). In addition, Boyd teaches that it is well established that lactobacilli can be readily transformed using available genetic engineering techniques (column 15). Boyd teaches that lactobacilli can be used as the delivery vehicle for a cyanovirin (columns 6-7 and 15-18). Boyd teaches that lactobacilli has been used against pathogenic bacterial or yeast infections of the urogenital tract based on the endogenous production of virucidal levels of H_2O_2 and/or lactic acid and/or other potentially virucidal substances (column 16). Boyd teaches that lactobacilli are prominent, nonpathogenic inhabitants of other

body cavities (column 15). However, Boyd does not specifically teach using modifying *Lactobacillus jensenii*.

Vallor et al. teach that *Lactobacillus jensenii* produces H_2O_2 and is a predominant lactobacilli in the vagina (page 1431).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Tagliabue et al, Schneewind and Steidler taken with Boyd and Vallor, to produce a genetically engineered *Lactobacillus jensenii* expressing a nucleotide sequence encoding a virus binding fragment to the vagina of a mammal. One of ordinary skill in the art would have been motivated to use *L. jensenii* as the recombinant bacterium for delivering a biologically active protein to the vagina of a mammal because *L. jensenii* is reported to colonize in the vagina as disclosed by Vallor (page 1431). In addition, one of ordinary skill in the art would have been motivated to combine the teaching to delivery a nucleotide sequence a viral binding fragment of cyanovirin-N using genetically engineered *Lactobacillus jensenii* to a mammalian mucosal surface cell in vitro to study the binding of cyanovirin-N to a viral pathogen as taught by Boyd (column 39). In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Tagliabue et al, Schneewind and Steidler taken with Boyd and Vallor, to produce a genetically engineered *Lactobacillus jensenii* a nucleotide sequence encoding a two domain soluble CD4 (2D-CD4). One of ordinary skill in the art would have been motivated to combine the teaching to delivery a nucleotide sequence encoding 2D-CD4 using

genetically engineered *Lactobacillus jensenii* to a mammalian's mucosal cells in vitro to study the binding of 2D-CD4 to a viral pathogen as taught by Boyd (columns 15-17 and 39). In view of the teaching of Tagliabue and Boyd and the teaching in the specification, one of ordinary skill in the art would have a reasonable expectation of success for producing the claimed *Lactobacillus jensenii*.

Therefore, the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-15, 18-21, and 25-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9

and 12 of copending Application No. 11/620,588. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a *Lactobacillus jensenii* bacterium recombinantly altered to express any biologically active protein when it is contacted with a pathogen. It is noted that claims of '588 claims differ only with respect to a broader scope of biologically active protein and specific elements to recombinantly alter bacterium set forth ion claims 1-5 7-21 are broadly encompassed those specifically claimed in claims 1-9 and 12 of '588. Therefore, the claims 1-5, 7-15, 18-21, and 25-26 of the instant application are encompassed by claims 1-9 and 12 of co-pending application '588.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Pallen et al . An embarrassment of sortases - a richness of substrates? Trends Microbiol. 2001, 9(3):97-102, IDS).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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